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Patterns of orthostatic hypotension and the evaluation of syncope

van Wijnen, Veera Kariina

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PART 1

ORTHOSTATIC BLOOD PRESSURE RECOVERY PATTERNS

CHAPTER 2

NONINVASIVE BEAT-TO-BEAT FINGER ARTERIAL PRESSURE MONITORING DURING ORTHOSTASIS: A COMPREHENSIVE REVIEW OF NORMAL AND ABNORMAL RESPONSES AT DIFFERENT AGES

Veera K. van Wijnen, Ciarán Finucane, Mark P.M. Harms, Hugh Nolan, Roy L. Freeman, Berend E. Westerhof, Rose A. Kenny, Jan C. ter Maaten, Wouter Wieling

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ABSTRACT

Over the past 30 years, noninvasive beat-to-beat blood pressure (BP) monitoring has provided great insight into cardiovascular autonomic regulation during standing. Although traditional sphygmomanometric measurement of BP may be sufficient for detection of sustained orthostatic hypotension, it fails to capture the complexity of the underlying dynamic BP and heart rate responses. With the emerging use of noninvasive beat-to-beat BP monitoring for the assessment of orthostatic BP control in clinical and population studies, various definitions for abnormal orthostatic BP patterns have been used. Here, age-related changes in cardiovascular control in healthy subjects will be reviewed to define the spectrum of the most important abnormal orthostatic BP patterns within the first 180 s of standing. Abnormal orthostatic BP responses can be defined as initial orthostatic hypotension (a transient systolic BP fall of >40 mmHg within 15 s of standing), delayed BP recovery (an inability of systolic BP to recover to a value of >20 mmHg below baseline at 30 s after standing) and sustained orthostatic hypotension (a sustained decline in systolic BP of ≥ 20 mmHg occurring 60–180 s after standing). In the evaluation of patients with light-headedness, pre (syncope), (unexplained) falls or suspected autonomic dysfunction, it is essential to distinguish between normal cardiovascular autonomic regulation and these abnormal orthostatic BP responses. The prevalence, clinical relevance and underlying pathophysiological mechanisms of these patterns differ significantly across the lifespan. Initial orthostatic hypotension is important for identifying causes of syncope in younger adults, whereas delayed BP recovery and sustained orthostatic hypotension are essential for evaluating the risk of falls in older adults.

INTRODUCTION

Orthostatic hypotension is defined as a sustained reduction in systolic blood pressure (BP) of at least 20 mmHg and/or diastolic BP of 10 mmHg within 3 min of standing or 60° head-up tilt. These criteria were originally defined in 1996 in a consensus statement sponsored by the American Autonomic Society and the American Academy of Neurology (1). In 2011, the consensus statement was expanded to include initial orthostatic hypotension (IOH), that is a transient BP decrease (>40 mmHg systolic BP and/or >20 mmHg diastolic BP within 15 s of standing) (2).

For routine assessment of orthostatic circulatory adjustments, intermittent BP measurement with a sphygmomanometer and monitoring of the heart rate (HR) are adequate. Serial BP and HR measurements in the supine position and after 2–3 min of standing provide a general assessment of the circulatory response to standing (3–7). However, such intermittent BP measurement is not appropriate for evaluation of conditions in which there are sudden transient changes in the circulation, such as the rapid changes that occur during standing, which can only be evaluated with continuous arterial BP measurement (4,5,8). In this context, continuous noninvasive measurement of finger arterial pressure (FinAP) enables detailed evaluation of autonomic cardiovascular control (4,5).

The aims of this review are as follows:

- to summarize the orthostatic adjustments in healthy subjects in the first 180 s after active standing in relation to age using noninvasive continuous FinAP monitoring;
- to compare the physiological mechanisms underlying short-term orthostatic adjustments reported in earlier studies (with small numbers of participants) and in large recently obtained epidemiological datasets from the Irish Longitudinal Study on Ageing (TILDA);
- to consider the pathophysiology and clinical relevance of the spectrum of abnormal initial orthostatic BP and HR responses.

Noninvasive continuous monitoring of FinAP

Noninvasive continuous measurement of FinAP was first applied in clinical settings in the 1990s (9). Several devices using this technology were developed over the years; however, as this is not relevant to the current review, the abbreviation FinAP is used to represent all these devices. In this review, we will focus exclusively on FinAP; other noninvasive continuous haemodynamic monitoring technologies (10) will not be discussed.

The FinAP method is based on dynamic (pulsatile) unloading of the finger arterial walls using an inflatable finger cuff with a built-in photoelectric plethysmograph (9,11,12). The finger cuff is connected to a wrist-worn unit containing a fast servo-controlled pressure system for the continuous adjustment of cuff pressure according to the changes in plethysmographic output. The cuff and wrist-worn unit are connected to a primary unit which holds the air pump, electronics and a computer (Fig. 1).

Noninvasive continuous FinAP recordings are similar in appearance to intra-arterial BP recordings and have been validated extensively as a reliable method to track changes in BP (10-17), but these two types of measurement are not identical (Fig. 2). This is because arterial waveforms in the finger differ from those in more central arteries (10). Systolic BP in the finger may be higher compared to invasive brachial BP whereas mean and diastolic BP will be lower (9,10). Recent studies suggest that pressure levels with FinAP measurement lie between invasively measured and auscultatory measured pressures, with FinAP measurements remaining accurate at low pressures (12,13). No differences were found between different age groups when comparing noninvasive and invasive arterial pressure measurements (9).

Haemodynamic parameters such as stroke volume, cardiac output (CO) and systemic vascular resistance (SVR) can be derived from the measured BP waveforms using model-based approaches (10,17). The FinAP techniques use mathematical modelling with a three-element Windkessel model (18) to estimate these parameters (17,19). This approach captures trends in variations in CO and SVR whilst absolute values are less accurate (19), requiring calibration with a suitable gold standard CO measurement technique (e.g. thermodilution or rebreathing) (20-22) (for details about technical aspects and reliability of FinAP measurements, see (11-17)).

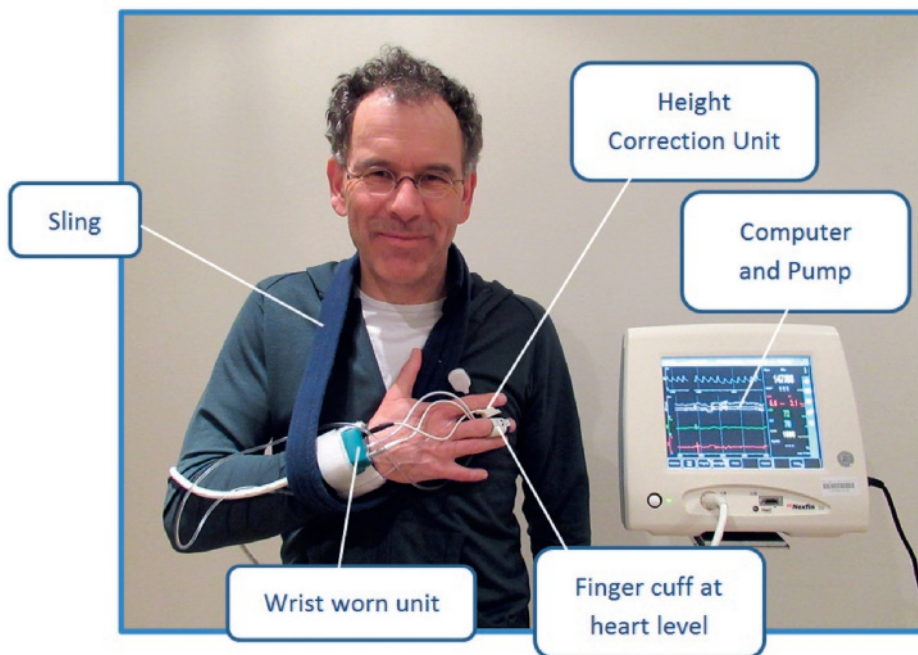


Fig. 1 Standing phase of the active lying-to-standing test performed with finger arterial pressure measurement. The finger cuff is shown around the middle finger with the height correction sensor attached. The finger cuff is connected to the wrist-worn unit, which is connected to a primary unit consisting of the air pump, electronics and a computer. The arm with finger cuff is held at heart level by a sling. The other part of the height correction unit is attached to the sling at heart level.

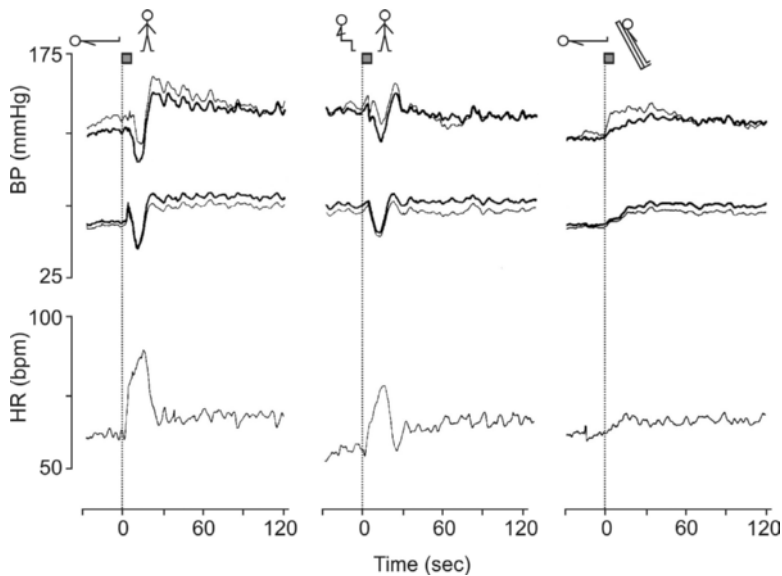


Fig. 2 Blood pressure (BP) and heart rate (HR) during three orthostatic manoeuvres. Group average intrabrachial (thick lines) and finger (thin lines) BP and HR responses in 11 male volunteers aged 22–40 years to three orthostatic manoeuvres (standing from supine, standing from sitting and tilting). The time needed to change posture is indicated at the top of the dotted line at $T = 0$ (from Imholz et al. 1990, with permission (86)).

Active stand protocol

Orthostatic stress can be assessed by standing up from a supine or sitting position or by head-up tilt testing. Here, we focus on the initial circulatory response induced by the natural, real-world stimulus, that is active standing after a 5- to 10-min supine resting period [see active stand protocol video: https://youtu.be/NwWFie1_ddU?t=397 (6:36–7:06). On passive tilting, the characteristic initial BP response is far less pronounced or even absent (Fig. 2). Head-up tilt will not be addressed in detail in this review. We will also focus on standing up from the supine and not from the sitting position (23,24), in line with almost all previously reported studies.

Haemodynamic adjustments in the first 180 s after standing up in healthy subjects: effects of age

It is useful to classify the short-term orthostatic circulatory response (first 180 s) in laboratory conditions according to the following criteria (4,25):

- the initial response (first 30 s);
- the early phase of stabilization (30–180 s upright).

The short-term orthostatic circulatory adjustments are governed almost exclusively by the neural control system. Crucial to interpreting the initial transients in BP and HR upon standing is the knowledge of time delays and the speed at which the autonomic system responds (i.e. the time constant). The time delay between baroreceptor afferent nerve stimulation and initiation of vagal slowing of HR is within one beat (approximately 0.5–0.6 s), and lowering of BP induced by sympathetic withdrawal begins after 2–3 s with full effects occurring at 10 s (26–30).

Initial response (first 30 s)

Pioneering work on the initial orthostatic circulatory responses in relation to age was performed by Jan Dambrink, a general practitioner, who together with his colleagues studied HR and noninvasive FinAP measurements in healthy 10- to 14-year-old children and healthy older adults in the setting of his general practice in the early 1990s (31–34). For these studies, 10- to 14-year-old children were recruited consecutively when they consulted the practice for minor ailments. They had no history of postural complaints or frequent fainting (33). Apparently healthy female and male subjects over 70 years were recruited from patients applying for a medical certificate for a driver's licence and from volunteers attending a local community centre. Subjects were active and independent, regularly performed physical exercise such as walking and cycling, and occasionally folk dancing, were not on medication and did not have diabetes mellitus or cardiopulmonary, neurological or other major systemic diseases. High BP was not an exclusion criterion. All subjects ate a normal diet without salt restriction (34).

Figure 3 shows the results from the first of these studies (32). Beat-to-beat HR changes in four different age groups were studied. In the youngest age group, HR increased abruptly towards a primary peak at around 3 s, increased further to a secondary peak at around 12 s, declined to a relative bradycardia at around 20 s and then gradually increased again. The primary HR peak (3 s) (Fig. 3) is due to reflex inhibition of cardiac vagal tone and may be attributed to an exercise reflex that operates when voluntary muscles contract (35). The more gradual secondary HR rise, starting at approximately 5 s, can be attributed to the fall in arterial pressure and diminished activation of arterial baroreceptors (Fig. 2) with further reflex inhibition of cardiac vagal tone and increased sympathetic outflow to the sinus. The subsequent decrease in HR is associated with the recovery of arterial pressure and is again mediated through the arterial baroreflex by an increase in vagal outflow to the sinus node (35,36). Figure 3 clearly shows that the initial biphasic HR response on active standing decreases with age; the primary peak at 3 s is no longer present in old age (32).

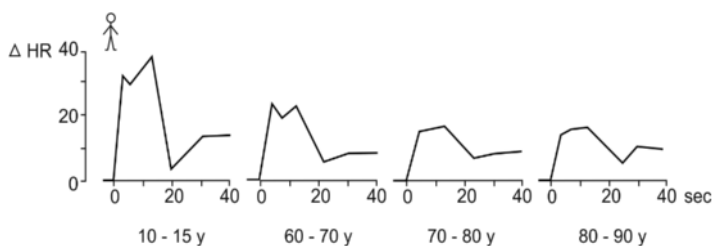


Fig. 3 Heart rate (HR) changes upon standing in children and young and older healthy adults. Change in HR (beats per min) in the first 40 s after active standing from the supine position (rest for 5 min) in four different age groups with 10 subjects per group (from Dambrink and Wieling 1987, with permission (32)).

Pulse wave analysis was subsequently used to determine the haemodynamic mechanisms underlying the initial fall in BP in healthy young adults (Fig. 4, middle panel) (37,38). Briefly, the muscular effort of standing compresses venous vessels in the legs and abdomen, causing an immediate translocation of blood towards the heart, thereby increasing right atrial pressure (37-39). The combination of an increase in venous return and a marked increase in HR results in an increase in CO. The maximum CO (increase of 24%) occurred at around 7 s after the onset of standing. Simultaneously, a drop in mean arterial pressure was observed, reflecting a pronounced fall (by 36%) in SVR (40). Very similar findings were reported by Tanaka and colleagues using ultrasound pulsed Doppler echocardiography in seven healthy volunteers aged 25–41 years (39). This would suggest that the magnitude of the initial BP decline that follows standing up is a reflection of hydraulic mechanical properties of the vasculature (leg muscle pumping and abdominal compression) and instantaneous vasodilatation.

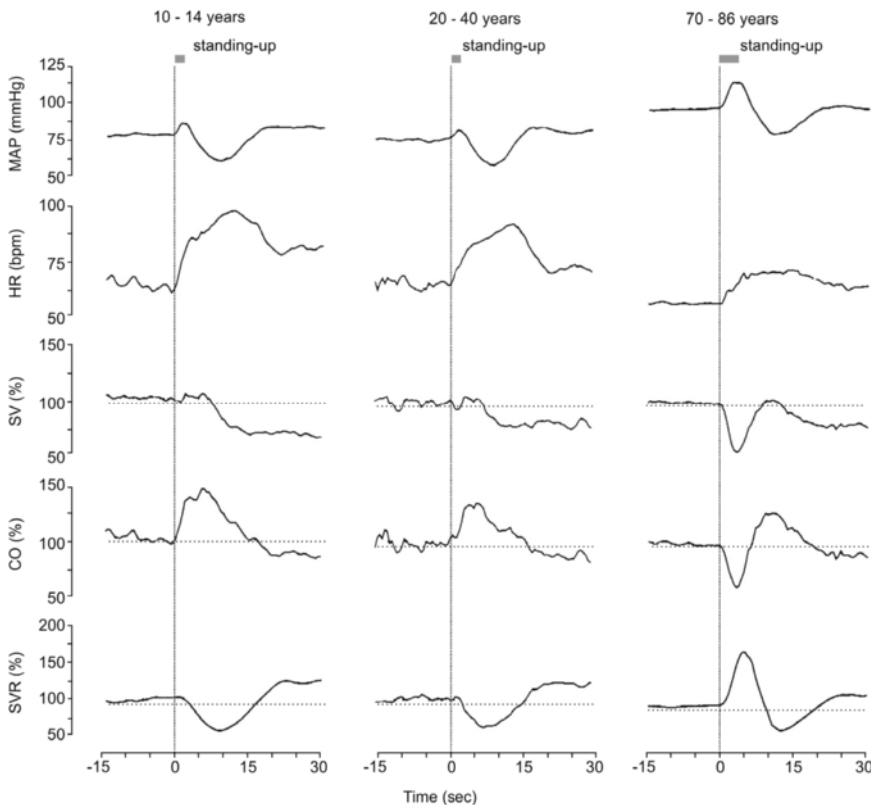


Fig. 4 The effect of age on the initial haemodynamic responses. Pulse wave analysis comparing the initial circulatory adjustment in 10 male teenagers, 10 young adults and 20 older male subjects (over 70 years). The time needed to change posture is indicated at the top of the dotted line at $T = 0$. SV, CO and SVR are expressed as percentage of change. MAP, mean arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; SVR, systemic vascular resistance (from Wieling and Karemaker 2013, with permission (4)).

Four factors have been proposed to explain the large fall in SVR that exceeds the CO response. First, rapid vasodilatation in the contracting leg muscles with the effort of standing (41,42). An active muscular effort to stand from lying down or squatting results in more marked IOH, compared with a passive change to upright posture (Fig. 2). This suggests that the vascular phenomena localized in the active lower limbs and abdominal muscles contribute to rapid vasodilatation and therefore a fall in SVR (41). Resistance vessels in skeletal muscles can dilate almost immediately following a brief (as little as 0.3 s) muscle contraction. This dilatation peaks approximately 4 s after a brief contraction and then returns to normal over the next 10–20 s (41,43).

Second, an increase in the arterio-venous pressure gradient in the lower limbs (43,44). This increase occurs via immediate elevation in lower limb hydrostatic pressure on the arterial side of the circulation, whilst the pressure on the venous side is initially low because venous vessels are emptied by leg and abdominal muscle contraction (24,36,44,45). However, this elevation in flow would be maximal at the moment the muscles used in standing up relax and then dissipate as the veins quickly refill. This does not correspond precisely with the time course of hypotension following the muscular effort as occurs in active standing.

Third, stimulation of cardiopulmonary receptors at the onset of whole-body exercise (38,39). Activation of cardiopulmonary receptors by an increase in right atrial pressure (10–15 mmHg) resulting from compression of venous vessels by the contracting legs and abdominal muscles may trigger an abrupt reflex withdrawal of sympathetic vasoconstrictor tone, and a subsequent fall in SVR (37,39,40). However, the time constant for vascular relaxation (delay of 2–3 s, full effect after about 10 s) (26–29,37) is too long to explain the immediate fall in SVR with a nadir at around 8 s in young adults (41).

Fourth, activation of arterial baroreceptors by the arterial pressure increase upon standing up (36). This does not play an important role in teenagers and young adults, because the immediate increase in BP is minimal (37,40). By contrast, immediate stimulation of arterial baroreceptors is clear in the elderly (Fig. 4).

It may be concluded that interpretation of the physiological factors involved in the initial fall in SVR is complex. A combination of mechanical factors is likely to be involved and the mechanism may be different depending on the length of the period of supine rest, the way a subject stands up and the age of the subject. Table 1 provides an overview of the BP nadir, BP recovery/overshoot and the transient HR changes between 0 and 30 s in the early studies (24,33–35,38) along with data from a healthy subsample of participants from TILDA (see next section for specific discussion relating to TILDA). In teenagers, young adults and older subjects, the BP nadir occurs 8–9 s after the onset of standing up. After the nadir, a rapid recovery of BP occurs presumably through arterial baroreflex-mediated vasoconstrictor activity (37,38,42,43). Recovery of BP reflects active functioning of the arterial baroreflex, the major mechanism involved in short-term BP regulation (38,42). The changes in HR follow the BP changes upon standing with a peak HR increase at around 12 s of 40 beats per min (bpm) in teenagers and 17 bpm in older subjects, with a reflex bradycardia at around 20 s to values similar to the supine control (Table 1 and Fig. 3). In healthy older adults, an overshoot may or may not be present with the peak HR and reflex bradycardia also reduced.

Using FinAP monitoring and pulse wave analysis, we were able to study the effect of age on the initial haemodynamic responses. The responses in 10- to 14-year-old children (Fig. 4, left panel) and older adults (Fig. 4, right panel) can be compared with the responses in young adults (Fig. 4, middle panel). There were no differences between female and male subjects in any of the age groups.

The circulatory responses in 10- to 14-year-old children and young adults were similar. The immediate increase in BP was very small (Fig. 4, left and middle panels) (33). Differences were found between older adults aged 70–86 years and the younger age groups. Standing up was accompanied by a large immediate temporary BP peak (19/24 mmHg); an abrupt decrease in stroke volume and increase in SVR were observed (Fig. 4, right panel) (34,46). This immediate BP increase can be attributed to combined effects on BP of straining and/or squeezing, kinking of blood vessels and finger/hand motion that accompanies the physical activity of standing up resulting in a mechanical increase in BP and/or SVR (36). The immediate BP rise in older adults was followed by a brief but marked drop in BP with a subsequent rapid recovery. From about 7 s after the onset of standing up, the cardiovascular response appeared similar to the responses in teenagers and young adults. However, it should be noted that the stimulus inducing the cardiovascular reflex responses must have been different in the older adults compared to the younger age groups, as standing up was accompanied by a pronounced and prolonged increase in BP, which implies a strong arterial baroreflex stimulus. Slowing of the heart is expected during baroreflex stimulation, but an immediate HR increase on standing was observed in Figs 2–4. However, such an acceleration is also observed at the onset of large mechanically induced increases in BP such as during coughing and straining. The acceleration may be explained by an exercise-induced response that operates when voluntary muscle contractions are performed (45). Thus in older subjects, baroreflex stimulation may play a role in the fall of SVR.

The magnitude of the nadir in BP in older subjects did not differ from that in teenagers and young adults in 'the Dambrink cohort' (Fig. 4 and Table 1). The hemodynamic mechanism underlying the fall in BP in the older adults was similar to that in teenagers and adults, that is mismatch between CO and SVR effects on arterial outflow (Fig. 4). However, compared to teenagers and young adults, the increase in CO was less pronounced and the fall in SVR less noticeable in older adults. At the end of the initial phase (30 s), systolic BP was at the level of the supine control and diastolic BP had increased beyond that level.

Table 1 Blood pressure (BP) and heart rate (HR) changes in healthy subjects in the first 30 s upon active standing after 5–10 min of supine rest

Study	Nadir BP/ T nadir	HRmax + Tmax HRmin + Tmin	HRmax - HRmin	Overshoot after initial BP drop/ T overshoot	Recovery at 30 s
	mmHg	bpm	bpm	mmHg	mmHg
Dambrink <i>et al.</i> , 1991 (33) <i>n</i> = 20 Age: 10–14 years	SBP: -22 ± 14 T = 8 ± 2 s DBP: -16 ± 7 T = 8 ± 2 s	HRmax: 40 ± 7 Tmax = 11 ± 1 s HRmin: 12 ± 11 Tmin = 20 s	28	SBP: 11 ± 9 DBP: 12 ± 6 T = 17 ± 3 s	SBP: 4 ± 11 DBP: 9 ± 6 HR: 18 ± 12 bpm
Borst <i>et al.</i> , 1982 (35) <i>n</i> = 43 Age: 20 ± 4 years	-	HRmax: 35 ± 10 Tmax = 12 ± 2 s HRmin: 3 ± 9 Tmin = 19 ± 2 s	32	-	-
Ten Harkel <i>et al.</i> , 1990 (24) <i>n</i> = 10 Age: 28 (22–40) years	SBP: -20 ± 12 T = 8 s DBP: -17 ± 6 T = 7 s	HRmax: 36 ± 7 Tmax = 12 s HRmin: 2 ± 12 Tmin = 20 s	34	SBP: 25 ± 11 T = 18 s DBP: 14 ± 4 T = 16 s	Recovery within 20 s
Sprangers <i>et al.</i> , 1991 (38) <i>n</i> = 8 males Age: 21–41 years	SBP: -25 T = 9 s DBP: -20 T = 8 s	HRmax: 25 Tmax = 13 s HRmin: 5 Tmin = 20 s	20	SBP: 30 T = 20 s DBP: 25 T = 20 s	SBP: 20 DBP: 15
Lindqvist <i>et al.</i> , 1997 (51) <i>n</i> = 23 Age: 35 ± 9 years	SBP: -20 ± 12	-	-	SBP: 15 ± 13 DBP: 15 ± 11	-
Imholz <i>et al.</i> , 1990 (34) <i>n</i> = 40 Age: 77 years	SBP: -26 ± 13 T = 9 s DBP: -12 ± 8 T = 10 s	HRmax: 17 ± 7 Tmax = 10 s HRmin: 6 ± 5 Tmin = 22 s	11	SBP: 11 ± 17 DBP: 8 ± 6 T = 24 s	SBP: -2 ± 17 DBP: 4 ± 7 HR: 7 ± 5 bpm
TILDA, 2017* <i>n</i> = 34 Age: 74 ± 4 years	SBP: -40 ± 17 T = 10 s DBP: -27 ± 12 T = 9 s	HRmax: 19 ± 8 Tmax = 11 s HRmin: 1 ± 10 Tmin = 23 s	11	-	SBP: -4 ± 19 DBP: -4 ± 12 HR: 6 ± 6 bpm
Range of the means	SBP: -20 to -40 T = 8 to 10 s DBP: -12 to -27 T = 7 to 10 s	HRmax: 17 to 40 Tmax = 10 to 13 s HRmin: 1 to 12 Tmin = 19 to 23 s	11 to 34	SBP: 11 to 30 DBP: 8 to 25 T = 16 to 24 s	SBP: -4 to 20 DBP: -4 to 15 HR: 6 to 18 bpm

Age is given as range, mean alone or mean ±SD. BP and HR values are given in means, with SD or range if available. Nadir BP is defined as the lowest BP within the first 15 s after standing up; HRmax is the highest HR upon standing; HRmin is the subsequent minimum; T indicates the (mean) time to reach nadir BP, HRmax, HRmin and BP overshoot. BP, blood pressure; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure; SD, standard deviation. *Unpublished data. Healthy subsample on no medications, with no known comorbidities and with available active stand data represents 1.5% of participants over 70 years in The Irish Longitudinal Study on Ageing population.

The early phase of stabilization (30–180 s upright)

An increase in baroreflex-mediated sympathetic outflow to resistance and capacitance vessels plays a key role in the stabilization of BP in the early phase of standing (42,47–50). On *average* little change in systolic BP and increases of 5–10 mmHg in diastolic BP occurred although the between-individual variability in haemodynamic adjustments was large (47). There is a close relationship between the BP values during recovery/overshoot and the values during 1–3 min of standing (51). A sustained decrease of >20 mmHg in systolic BP during the early phase of stabilization is uncommon in fit healthy subjects (32,34).

The systolic and diastolic BP changes after 1 min of standing in teenagers and young adults in the above-mentioned studies were very similar to those in the healthy older adults. Systolic and diastolic BP increased on average between 30 and 120 s in the older adults (Table S1).

The HR increase after 1–3 min of standing depends on vagal withdrawal and increased activity of the sympathetic nervous system (47). This orthostatic rise in HR decreased with age with values of around 25 bpm in children and around 10 bpm in older adults (4,32,34,52,53). This was already clear at 30 s after standing up (Fig. 4).

Comparison of data from TILDA and from the earlier physiological studies

Next, the age-related changes in orthostatic circulatory adjustments after active standing will be described based on recent epidemiological evidence from TILDA (participants ≥50 years). We will also provide comparisons with previous detailed physiological studies (32,34) in adults aged 50 years and above.

TILDA is a large prospective population study of 8175 community-dwelling adults aged ≥50 years (54–56). A FinAP active stand test is included as part of a comprehensive health assessment at study entry and at regular intervals thereafter. Institutionalized adults or those with cognitive impairment or dementia are excluded; otherwise, the TILDA data represent an adult population and as such include a wide spectrum from healthy to disabled. For the purposes of comparison with studies by Dambrink and colleagues in healthy subjects (32,34), we derived a ‘healthy’ subsample from TILDA. Active stand data were available for 4475 participants of whom 502 (11.2%) were ‘healthy’, defined as physically and socially active, independent, without cardiovascular (excluding hypertension) or other physical or cognitive health conditions and not taking any medications. HR and BP responses from this subsample are shown in Fig. 5.

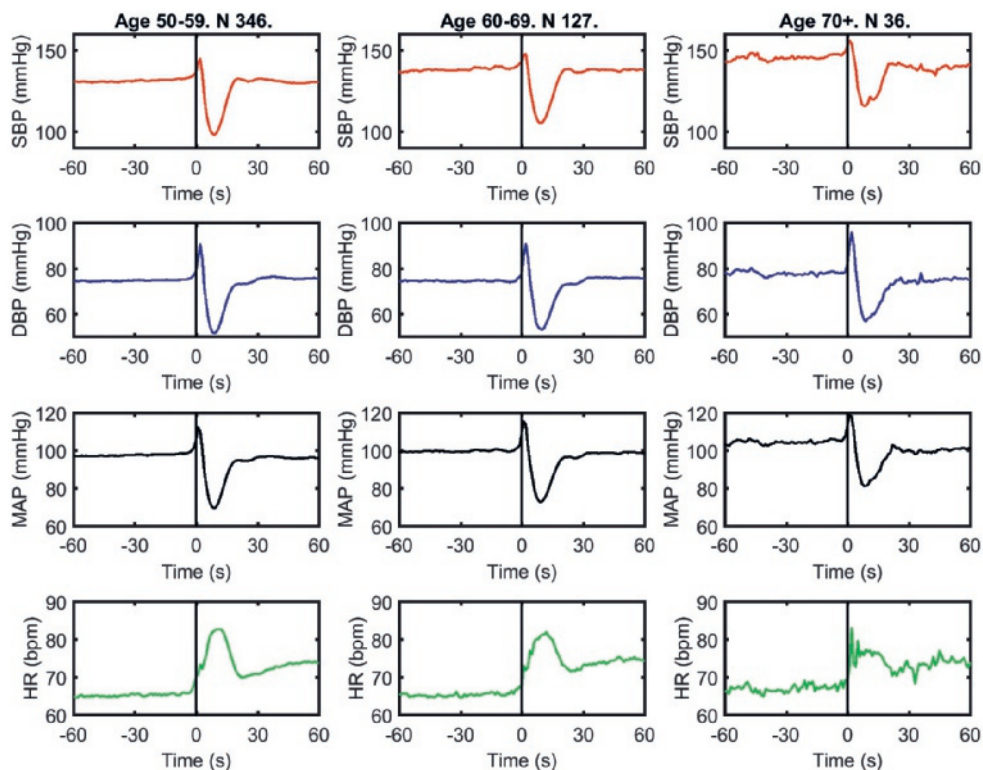


Fig. 5 Effect of age on orthostatic blood pressure in a healthy subsample of The Irish Longitudinal Study on Ageing ($n = 509$). Blood pressure and heart rate (HR) are assessed with continuous noninvasive blood pressure measurement. The changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and HR following standing are divided into three age groups (50–59, 60–69 and ≥ 70 years). The last 60 s in the supine position until 120 s after standing up are shown. Raw data are shown sampled at 1 Hz with automated artefact beat removal.

Initial response (first 30 s)

In the healthy subsample from TILDA (aged ≥ 70 years), standing is accompanied by a large immediate temporary BP peak (Table 1). This immediate peak is far less pronounced in teenagers and young adults (Figs 4 and 5). The immediate BP rise is followed by a brief but marked drop in BP with a subsequent recovery. The decreases in systolic and diastolic BP were larger in the TILDA healthy subsample compared with the Dambrink cohort (40/27 mmHg vs. -26/12 mmHg) (34). Both studies showed on average a rapid recovery to supine values within 20–30 s (Figs 4 and 5), although recovery of BP was delayed in 24% of subjects (aged ≥ 70 years) in the TILDA healthy subsample (see below). Peak initial HR values after standing occurred at approximately 10–12 s in both cohorts, and the magnitude of the peak HR responses compared with baseline were similar (Table 1 and Figs 3–5).

In the TILDA healthy subsample, the magnitude of the HR responses declined with age (23 bpm at 50–59 years vs. 19 bpm at ≥ 70 years). HR declined and the minimum difference from

baseline occurred at 20–24 s in both series. HR values stabilized at about 5–10 bpm above baseline after 30 s.

The early phase of stabilization (30–180 s upright)

Systolic BP stabilized to -5 mmHg at 60 s and -1 mmHg at 120 s after standing in the TILDA healthy subsample compared to 2 and 11 mmHg in the Dambrink cohort, respectively (Fig. 5 and Table S1). In the Dambrink cohort, systolic and diastolic BP increased on average between 30 and 120 s; the variation in values was large in both cohorts. A small proportion of the TILDA healthy subsample (2.3%) had a sustained drop in systolic BP of ≥ 20 mmHg up to 2 min after standing indicative of orthostatic hypotension, whilst 5.0% (2/40) had similar drops 2 min after standing in the Dambrink cohort. In the TILDA healthy subsample, HR differences from baseline after 30 s declined with age – similar to Dambrink's findings.

We conclude that the orthostatic adjustments in the Dambrink cohort and the healthy TILDA subsample are similar. Of note, overall only 11.2% of subjects in the TILDA population were considered 'normal' according to the original criteria of Dambrink and colleagues and this proportion was even lower (1.5%) in those over 70 years of age. We therefore propose that these subjects are 'super agers'.

Spectrum of abnormal circulatory responses during first 180 s after standing up

Next, we will consider the application of the physiological insights obtained from FinAP studies to patient care, focusing on the spectrum of abnormal BP and HR responses that are most frequently encountered in clinical practice, that is IOH, delayed BP recovery and sustained orthostatic hypotension (Fig. 6). Impaired short-term HR and BP control as risk factors will not be considered in detail. For classification of the spectrum of abnormal BP responses, we will use the systolic BP cutoff only, because (i) the absolute magnitude of changes in systolic BP is larger than that of diastolic BP and therefore easier to measure; (ii) an abnormal orthostatic fall in diastolic BP without an abnormal fall in systolic BP is rare amongst patients with syncope and orthostatic intolerance (57,58); and (iii) an abnormal fall in diastolic BP with a minor or no fall in systolic BP will increase pulse pressure. Because the main determinants of brain blood flow are the absolute level of arterial pressure and the pulse pressure (59), an isolated fall in diastolic BP is not likely to induce significant hypoperfusion of the brain. Accordingly, it has been shown that symptoms of orthostatic intolerance such as lightheadedness or (pre)syncope may be dependent on systolic BP and not on diastolic BP decline (60).

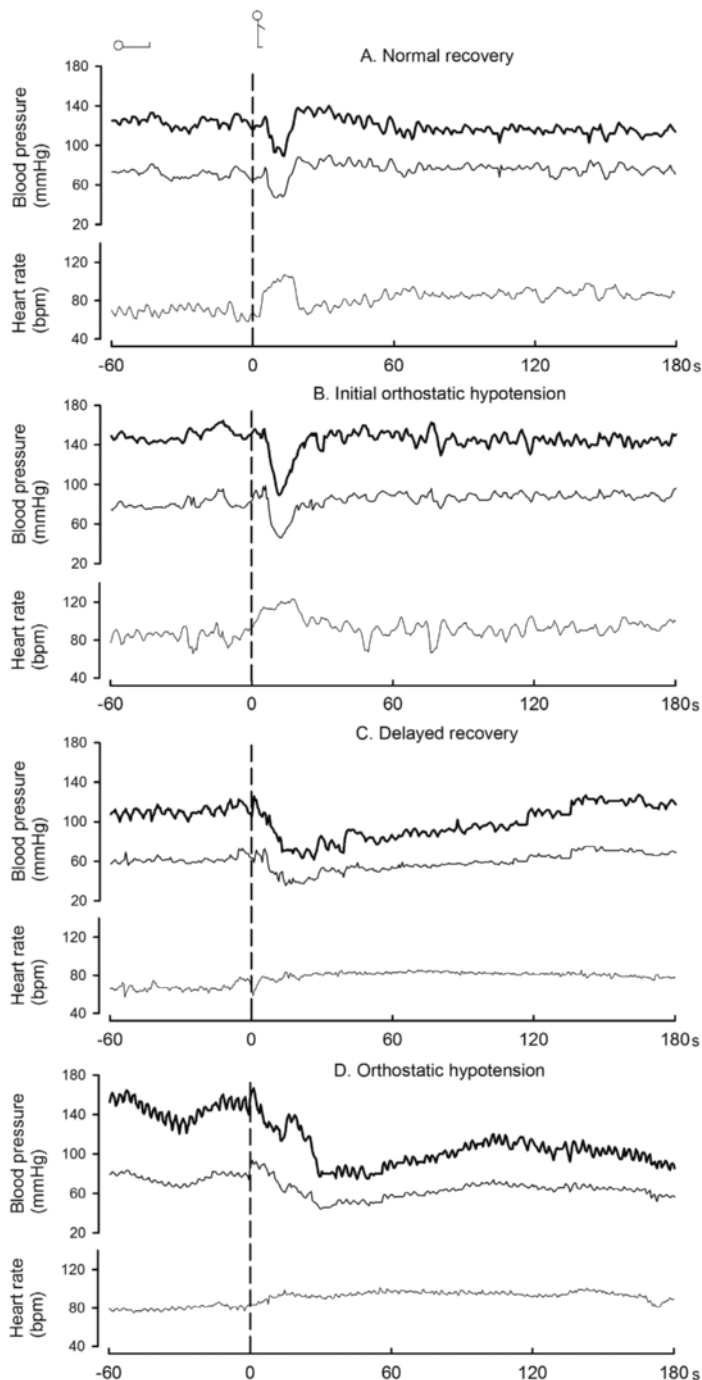


Fig. 6 Spectrum of normal and abnormal blood pressure (BP) and heart rate responses during the first 180 s after standing. Measurement of orthostatic BP with continuous noninvasive measurement in four subjects. The last 60 s in the supine position and 180 s of standing are illustrated. Dashed vertical lines indicate the onset of the active stand. Normal orthostatic BP recovery (a), initial orthostatic hypotension (systolic BP decrease >40 mmHg within 15 s of standing, with recovery to baseline within 30 s) (b), delayed BP recovery (systolic BP fall of >20 mmHg at 30 s of standing, but not meeting the criteria of classical orthostatic hypotension) (c) and classical orthostatic hypotension (sustained fall in systolic BP of ≥ 20 mmHg between 60 and 180 s of standing) (d) are illustrated.

Normal initial BP and HR response

A normal initial BP response on standing consists of an asymptomatic transient fall in BP with a nadir at around 8 s followed by a rapid recovery and a recovery/overshoot of BP at around 20 s. An accompanying normal initial HR response including an immediate HR increase, an HR peak and a subsequent bradycardia indicates intact afferent and efferent cardiac vagal and sympathetic cardiac and vasomotor baroreflex pathways (4). The magnitude of the initial HR response decreases with age, and reference values have been published (4,52,53). Reflex bradycardia is an arterial baroreflex response to the recovery and overshoot of BP and is mediated by a sudden decrease in vagal outflow. Thus, reflex bradycardia can be used to assess the cardiac vagal baroreflex arc in the same way as the reflex bradycardia induced by the Valsalva manoeuvre (61). Impaired Valsalva baroreflex sensitivity has been shown to be a potent and independent predictor of cardiovascular death in a population-based sample of middle-aged men without a history of major cardiovascular complications (62). Accordingly, McCrory et al. (63) have recently shown in a study of 4365 subjects aged 62.8 years that reflex bradycardia as measured using speed of HR recovery during standing is an important predictor of mortality.

By consensus, a transient decrease in systolic BP of >40 mmHg within 15 s of standing is considered abnormally large (2). BP nadirs in the early studies summarized in Table 1 for teenagers and young adults range from -20 to -26 mmHg for systolic BP. The SD of the systolic BP nadir is large, which can be attributed to a skewed distribution with large falls in BP in some healthy subjects (51,64). Thus, overall a cut-off of 40 mmHg in systolic BP seems reasonable for teenagers and young adults. The results of the healthy TILDA subsample (mean fall of 40 mmHg in systolic BP) suggest that a different cut-off should be considered for subjects ≥ 50 years.

The recovery of BP after the nadir occurs almost without exception within 30 s of standing, and a BP of >20 mmHg below baseline at 30 s is very rare in teenagers and adults (Table 1 and Figs 2, 4 and 5) (8,24,36,38,53,64). Similarly, in both the Dambrink and TILDA healthy subsample cohorts (super agers), recovery also occurred on average within 30 s although there are exceptions to this in old age (see above). In the full TILDA population sample, the prevalence of delayed BP recovery rose dramatically with age (see below).

IOH

IOH is defined here as a transient decrease in systolic BP of >40 mmHg within 15 s of standing. IOH is a measurement result, and it is irrespective of symptoms of orthostatic intolerance (43,57). Sustained orthostatic hypotension (a sustained fall of ≥ 20 mmHg in systolic BP) is not observed.

Taking complaints of patients as a starting point, a presumed diagnosis of IOH is an important issue because it is a common reason for referral to an emergency setting or a syncope unit. In a fainting assessment study (mean patient age 53.0 years), there was a higher incidence of IOH as a primary diagnosis (3.6%) than of situational syncope, that is micturition (2.6%), defaecation (0.4%) and cough syncope (1.6%) (65). Complaints of light-headedness, visual disturbances and/or (near) loss of consciousness shortly after standing are the most frequent orthostatic complaints in young subjects (44). Such spells of light-headedness are characterized by their time of onset

(5–10 s after standing up) and short duration (disappearance within 20–30 s). Patients have often walked a few steps before (near) fainting occurs (43,44,57). Symptoms instantaneously disappear after lying down (8,33,44,57,66). The complaints are generally attributed to retinal and cerebral hypoperfusion due to a transient fall in systemic BP. In severe cases, syncope may occur (67).

Considering the lack of malignant causes of syncope in young subjects with complaints of IOH, a typical clinical history is considered sufficient to reach a high likelihood (80–100% certain) of diagnosis (44,57,68). The additional role of diagnostic testing for IOH was addressed in a recent study (57). IOH was the clinical diagnosis, based on history taking alone in 26/371 (7%) teenagers and young adults with (near) syncope referred to a syncope clinic. An abnormally large initial fall in systolic BP (>40 mmHg) was present in only 15/26 (58%) of these patients during additional orthostatic BP testing. BP recovered within 30 s. The physiological mechanisms underlying IOH in these young patients varied. A fall in both CO and SVR may occur at the moment of the BP nadir (57). Of note, Tanaka et al. (69) have described IOH with delayed recovery of BP in teenagers with a tendency towards vasovagal fainting.

A clinical history of IOH is seen in older patients using medications that interfere with vasoconstrictor mechanisms, such as alpha-blockers for prostate hyperplasia (70), central sympathetic outflow blocking agents (71) and psychiatric medications (43). In older adults IOH may also be associated with a delayed BP recovery in some conditions (60,72). A large initial BP fall and a slow recovery is also found in patients with surgical denervation of the carotid baroreceptors (surgery to remove carotid body tumours) (73) and in patients with carotid sinus hypersensitivity (74,75). This abnormality is to be expected because the carotid baroreceptors are essential for adjustment to rapid changes in BP (4,28).

Romero-Ortuno et al. (76) conducted a study in 224 older adults (mean age 72.6 years) and found that 62 subjects (28%) reported symptoms of orthostatic intolerance upon standing during a standing test. The initial mean systolic BP fall in symptomatic patients was larger than in the asymptomatic group (40.8 ± 19.1 vs. 32.1 ± 17.4 mmHg). It is important to note that the nadir values were computed as a 5 s average, meaning that a beat-to-beat BP drop would have been larger and within the range of IOH for the symptomatic individuals. Patients with a delayed recovery of systolic BP to baseline were more likely to experience symptoms than patients with a fast recovery. A fall in diastolic BP alone was not associated with symptoms (76).

In the full TILDA study (4475 subjects ≥ 50 years), symptomatic IOH during testing was found in 32.9% of subjects (3.6% of men and 30.4% of women), with no age gradients observed, that is 35.0% in the 50–59 years age group versus 29.8% in those ≥ 80 years (77). Although no age gradient in the prevalence of IOH was evident, there was a marked age-related variation with wide confidence intervals in the older cohort. Furthermore, in cross-sectional or longitudinal follow-up (2 years), IOH (based on BP drops of 40/20 mmHg only) was not associated with adverse events such as falls or syncope (78). Therefore, IOH is not necessarily an attributable cause of syncope or falls in older adults.

Delayed BP recovery

In the literature, delayed recovery of orthostatic BP has been defined in many ways and related to different clinically relevant outcomes (76-80). Briefly, a delayed BP recovery is the inability of systolic BP to recover to ≥ 20 mmHg below baseline value at 30 s of standing. Recovery of BP occurs within 3 min of standing and therefore does not meet the criteria of the consensus on orthostatic hypotension (2). In certain individuals, delayed BP recovery may also be accompanied by an abnormally large initial BP drop, that is IOH (76,79,80). The prevalence of delayed BP recovery is between 15.6% and 54.0%, depending on the age group, population and definition applied (76,77,79,81).

In older adults with cardiovascular or other diseases and in patients receiving medications, a BP of ≥ 20 mmHg below supine control at 30 s is a common finding, especially amongst older patients (76,77,79,80). In the full TILDA cohort, there was a marked age gradient in the proportion with BP that failed to stabilize within 40 s of standing, from 9.1% of the 50- to 59-year-old subjects to 41.2% of those ≥ 80 years (77). Failure of systolic BP to stabilize by 40 s was significantly associated with increased relative risk of unexplained falls 2 years later with trends towards an increased relative risk of all-cause and injurious falls (78). Delayed recovery is also associated with poor cognitive function (82) and accelerated transition to dementia from mild cognitive impairment (83).

Classical orthostatic hypotension

Classical orthostatic hypotension is defined here as a sustained systolic BP decline of ≥ 20 mmHg within 3 min of standing (58). FinAP measurement has the advantage of detecting a continuous/sustained BP fall matching the definition of orthostatic hypotension from 60 to 180 s of standing, that is a fall of ≥ 20 mmHg in systolic BP at 60 s standing that is sustained. Findings from the Dambrink cohort and TILDA samples suggest that a 20 mmHg fall in systolic BP is a reasonable cutoff for orthostatic hypotension.

Intermittent measurements with traditional sphygmomanometer or semi-automatic electronic devices each take 15–45 s to perform. It is also worth noting that after each measurement, another measurement cannot be started for 1 min (to allow recovery of blood flow in the arm). Therefore, this limits the number of measurements that can be performed within a short timeframe. The mechanism underlying classical orthostatic hypotension can be either a decrease in effective circulating blood volume (e.g. due to haemorrhage, vomiting or diarrhoea) or impaired vasoconstriction (neurogenic orthostatic hypotension in patients with autonomic failure). If an obvious cause is not found (idiopathic), neurogenic orthostatic hypotension is assumed to be present (84). However, the data to support this view come mainly from autonomic units. Data from other settings are currently not available.

In the full TILDA series, failure to stabilize BP throughout a 2 min stand (sustained systolic BP decline of ≥ 20 mmHg and/or diastolic BP of ≥ 10 mmHg) was defined as orthostatic hypotension. Orthostatic hypotension was prevalent in 6.9% of subjects (mean age 62 years) with the prevalence rising from 3.2% (1.9–4.5%) in men aged 50–59 years to 18.9% (6.1–31.7%) in men over 80 years (77). Of note, orthostatic hypotension was associated with all-cause (incidence rate ratio

1.40), unexplained [relative risk (RR) 1.81] and injurious falls (RR 1.58) during the subsequent 2-year follow-up period (78).

The data from the population studies (60,76-78,80) suggest that it is not the magnitude of the initial fall in BP, but the duration of the period of hypotension caused by delayed recovery after the BP nadir (i.e. the hypotensive load) that is the key factor for symptomatic cerebral hypoperfusion. The anoxic reserve time of the brain is 6–8 s and a systolic BP below 60 mmHg at heart level exceeding that time window can be expected to lead to falls/syncope (67). Of note, with systolic BP values below 60 mmHg at heart level, cerebral autoregulation is no longer active (59). The findings of a study of the initial BP response by Lewis et al. (42) in healthy subjects given the alpha-blocker prazosin strongly support this notion. Future studies examining cerebral oxygenation determined using transcranial Doppler ultrasound and/or nearinfrared spectroscopy (85) should assist in further exploring this suggestion.

What can be learned from continuous noninvasive monitoring of FinAP in the first 180 s after standing?

Cardiovascular stress imposed by standing provides a unique opportunity to understand cardiovascular autonomic regulation in health and disease. Here, we have provided a comprehensive overview of insights we have gained over the past 30 years from continuous noninvasive monitoring of FinAP during standing. The conditions of a physiological study in a cardiovascular laboratory in a small number of subjects are different from those of large-scale epidemiological studies. We compared the results regarding physiological mechanisms in a healthy subsample of TILDA including subjects ≥ 50 years with findings from earlier detailed physiological studies in teenagers and healthy active older adults (32-34). The results are similar. This gives us a strong foundation to define normal and abnormal BP and HR responses across the lifespan. Figure 7 summarizes the important aspects of evaluation of orthostatic BP and HR patterns and their clinical relevance. In young subjects, IOH is common and is often a cause of (pre)syncope. In the older population, delayed BP recovery and sustained orthostatic hypotension are more common and are risk factors for falls, injuries and cognitive decline. Recognition of IOH, delayed BP recovery and sustained orthostatic hypotension is essential in the evaluation of patients with falls and (pre)syncope.

This review is dedicated to the memory of two great friends and scientists, Jan H. A. Dambrink (18 September 1940 – 4 December 4 2006) and Karel H. Wesseling (23 April 1935 – 4 September 2014).

Conflict of interest statement

BEW was supported by NWO-VICI (2002406) and has previously worked for Edwards Lifesciences, Amsterdam, the Netherlands. All authors declare no conflict of interests.

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The clinical use of analysing orthostatic blood pressure and heart rate changes

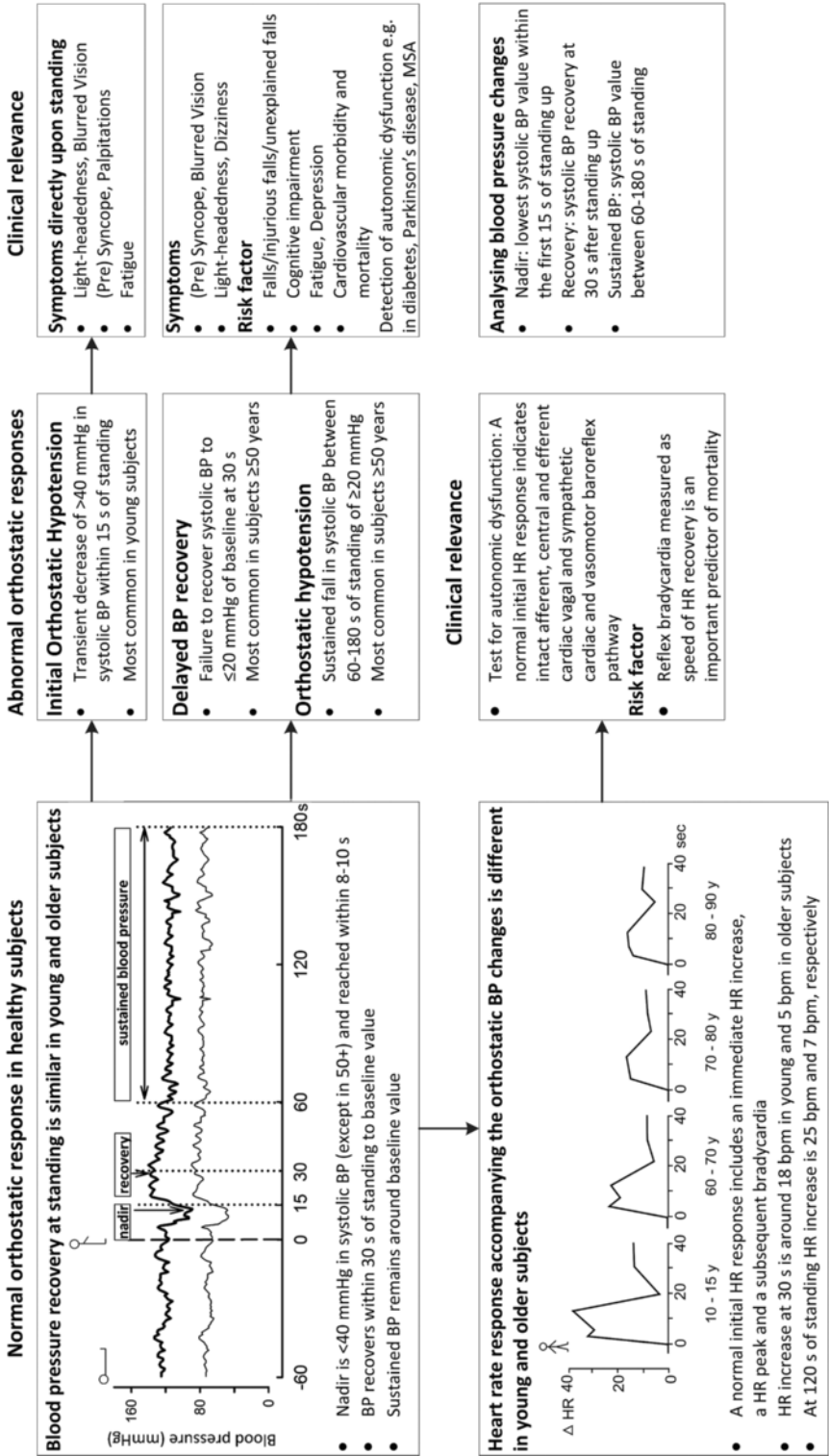


Fig. 7 The clinical use of analysis of orthostatic blood pressure (BP) and heart rate (HR) changes. An overview of the most important aspects of the normal and abnormal orthostatic BP and HR changes during the first 180 s of standing and their clinical relevance. MSA, multiple system atrophy.

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Table S1 Blood pressure and heart rate changes in healthy subjects during early steady state (30–120 s) upon active standing after 5–10 min of supine rest.

Study	30 s after standing	60 s after standing	120 s after standing
Dambrink <i>et al.</i> , 1991 (33) <i>n</i> = 20 Age: 10–14 years	SBP: 4 ± 9 mmHg DBP: 9 ± 6 mmHg HR: 18 ± 12 bpm	SBP: 2 ± 7 mmHg DBP: 10 ± 7 mmHg HR: 24 ± 14 bpm	SBP: 3 ± 7 mmHg DBP: 11 ± 5 mmHg HR: 25 ± 11 bpm
Imholz <i>et al.</i> , 1990 (34) <i>n</i> = 40 Age: 77 years	SBP: -2 ± 17 mmHg DBP: 4 ± 7 mmHg HR: 7 ± 5 bpm	SBP: 2 ± 17 mmHg DBP: 7 ± 7 mmHg HR: 10 ± 7 bpm	SBP: 11 ± 21 mmHg DBP: 12 ± 8 mmHg HR: 7 ± 6 bpm
TILDA 2017* <i>n</i> = 34 Age: 74 ± 4 years	SBP: -4 ± 19 mmHg DBP: -4 ± 12 mmHg HR: 6 ± 6 bpm	SBP: -5 ± 21 mmHg DBP: -3 ± 11 mmHg HR: 7 ± 5 bpm	SBP: -1 ± 21 mmHg DBP: -4 ± 11 mmHg HR: 5 ± 9 bpm

Age is given as range, mean alone, or mean \pm SD. Blood pressure and heart rate values are given as means \pm SD. Blood pressure was measured continuously noninvasively during 5–10 min in the supine position and for a minimum of 2 min during active standing. DBP, diastolic blood pressure; HR, heart rate; HRHRBP, systolic blood pressure; SD, standard deviation. *Unpublished data. Healthy subsample on no medications, with no known comorbidities and with available active stand data represents 1.5% of participants over 70 years in the Irish Longitudinal Study on Ageing population.

